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SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO BOX 142950 GAINESVILLE, FL 32614-2950			HISSONG, BRUCE D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

Formal Matters

1. Applicant's response/remarks and amended claims were received on 6/14/2006 and have been entered into the record.

2. The amendments to the claims have cancelled claims 1-12 and have added new claims 13-33. Therefore, claims 13-33 are currently pending.

3. The previous amendments, submitted on 2/21/2006, were found to be non-responsive as set forth in the notice mailed on 5/15/2006, because new claims 13-20 were drawn to methods of treating disease or methods of antagonizing RANTES activity, whereas originally examined claims 6-12 were drawn to a composition of RANTES polypeptides, and specifically a composition of the RANTES polypeptide defined by SEQ ID NO: 1. However, in light of the fact that previously examined claim 12 was drawn to a method of orally administering a RANTES polypeptide, new claims 21-33, which also read on methods of orally administering a RANTES polypeptide, will be examined as commensurate with the originally elected invention. Furthermore, upon further reconsideration, and taking into account that claims 13-20 essentially read on methods of orally administering a RANTES polypeptide, these claims will also be examined with claims 21-33. It should be noted that methods of treating disease (claims 13-16), methods of antagonizing RANTES activity (claims 17-20), and methods of orally administering a RANTES polypeptide (claims 21-33) could be considered independent and distinct inventions because each method has a different purpose/goal. However, for the reasons set forth *supra*, the claims will be examined together because they all ultimately read on methods of oral administration of RANTES polypeptides.

4. Therefore, claims 13-33 are the subject of this office action.

5. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 11/3/2005.

Information Disclosure Statement

The information disclosure statement received on 2/21/2006 has been considered by the Examiner. Citations F2, R6, and R7 were not considered because they are duplicate submissions of references that were cited in the information disclosure statement received on 7/11/2005.

Claim Objections

Objection to claim 9, as set forth on page 3 of the office action mailed on 11/3/2005, is withdrawn in response to Applicant's cancellation of the claim.

Claim Rejections - 35 USC § 112, first paragraph – enablement

Rejections withdrawn

1. Rejection of claims 6-8 and 10-12 under 35 USC § 112, first paragraph, regarding lack of enablement for polypeptides with less than 100% identity to the polypeptide of SEQ ID NO: 1, and mutants with "at least one non-conservative mutation in the 40's dibasic site", as set forth on pages 3-6 of the prior office action mailed on 3/1/2006, is withdrawn in response to Applicant's cancellation of the claims.

Rejections necessitated by amendment

2. Claims 13-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of orally administering a RANTES polypeptide of SEQ ID NO: 1 or SEQ ID NO: 5, does not reasonably provide enablement for oral administration of any other RANTES polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims of the instant invention are drawn to oral administration of RANTES polypeptides to an individual (claims 21-33), and methods of administering RANTES polypeptides for the purpose of treating a disease (claims 13-16) or antagonizing RANTES

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activity (claims 17-20). Claims 13, 17, and 21 recite administration of a polypeptide having at least 90% homology with the wild-type molecule, and also comprising at least one non-conservative mutation in the 40's dibasic site and having a reduced GAG-binding activity. As written, the breadth of these claims is excessive because the claims read on administration of any RANTES polypeptide that is at least 90% homologous to the wild-type molecule as long as it has at least one mutation in the 40's dibasic site. The claims are further broad because they read on the treatment of any autoimmune, inflammatory, and/or infectious disease, and also on antagonism of all possible RANTES biological activities. The specification provides guidance and examples showing that administration of the polypeptides of SEQ ID NO: 1 and SEQ ID NO: 5 are effective in relieving symptoms of multiple sclerosis, and is thus enabling for administration of these polypeptides for treatment of multiple sclerosis. However, the specification does not provide guidance showing that these polypeptides are capable of treating all possible viral or bacterial diseases. The specification also does not provide guidance or examples showing that any other polypeptide with at least 90% homology to wild-type RANTES and containing at least one mutation in the 40's dibasic site and having reduced GAG-binding activity, can be administered to an individual and still be effective in treating any disease, including autoimmune or inflammatory diseases, or all possible bacterial or viral infections. One of ordinary skill in the art would not be able to predict which of the amino acids of wild-type RANTES, in addition to at least one residue in the 40's dibasic site, could be substituted or otherwise mutated and result in a polypeptide which retains desired biological activities. As set forth in the previous office action mailed on 11/3/2005, Luck *et al* teaches that conservative amino acid changes can alter the biological activity of a protein by at least 90%, and therefore a skilled artisan would not be able to predict the effect of mutating any amino acid of wild-type RANTES. There is no guidance in the specification that teaches which regions or residues of wild-type RANTES must be conserved in order to retain biological function when the protein is orally administered, and therefore a person of ordinary skill in the art would not be able to predict which of the many possible RANTES mutants that are at least 90% homologous to wild-type RANTES and have at least one non-conservative mutation in the 40's dibasic site could be orally administered, or be effective in treating disease or antagonizing all possible RANTES activities. Similarly, other than multiple sclerosis, one of ordinary skill in the art would not be able to predict which of the many possible autoimmune, inflammatory, and/or infectious diseases could be treated by administration of any RANTES polypeptide that is at least 90%

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homologous to wild-type RANTES with at least one mutation in the 40's dibasic region and having reduced GAG-binding activity. Thus, a person of ordinary skill in the art would require further, undue experimentation in order to make all possible RANTES mutants that are at least 90% homologous to wild-type RANTES, and then test them for the ability to be orally administered to an individual for treatment of any autoimmune, inflammatory, or infectious disease, or antagonism of all possible RANTES activities.

In summary, the breadth of the claims is excessive because they read on methods of orally administering to an individual for purposes of treating any autoimmune, inflammatory, or infectious disease, or antagonizing all possible RANTES activities. The breadth of the claims is also excessively broad because they read on oral administration of any RANTES polypeptide that is mutated in any position, as long as the polypeptide is at least 90% homologous to the wild-type polypeptide and has at least one mutation in the 40's dibasic site and has a reduced GAG-binding activity. Furthermore, the specification lacks guidance or examples showing that any RANTES mutant other than SEQ ID NOs 1 and 5 can be administered to an individual, or is effective in treating the symptoms of any disease other than multiple sclerosis. Due to the unpredictability inherent in the art as it relates to the instant invention, a skilled artisan would require further, undue experimentation in order to make and use any RANTES polypeptide, other than those of SEQ ID NOs 1 and 5, and use the polypeptide to treat any autoimmune, inflammatory, or infectious disease in methods that are commensurate in scope with the claims. Therefore the claims do not meet the enablement requirements as set forth in 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejections withdrawn

1. Rejection of claims 6-8 and 10-12 under 35 USC § 112, first paragraph, regarding lack of written description for polypeptides with less than 100% identity to the polypeptide of SEQ ID NO: 1, mutants with “at least one non-conservative mutation in the 40's dibasic site”, and “mutants and their muteins”, as set forth on pages 7-9 of the prior office action mailed on 3/1/2006, is withdrawn in response to Applicant's cancellation of the claims.

Rejections necessitated by amendment

2. Claims 13-33 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of orally administering a RANTES polypeptide, wherein said RANTES polypeptide has at least 90% homology to wild-type RANTES, contains at least one mutation in the 40's dibasic region, and has reduced binding activity. The methods are further drawn to treatment of any autoimmune, inflammatory, or infectious disease by administration of said RANTES polypeptides. The claims do not require the RANTES polypeptides of the instant invention to have any biological activity other than reduced GAG-binding activity, nor any particular structure other than having at least one mutation in the 40's dibasic site. Although the instant specification discloses examples of polypeptides that meet these limitations (for example, SEQ ID NOs 1-6), the claims read on oral administration of a RANTES polypeptide that can be mutated in any position(s), as long as the resulting polypeptide has at least 90% homology to wild-type RANTES and has reduced GAG-binding activity. Additionally, SEQ ID NOs 1 and 5 exhibit 95% or greater homology to wild-type RANTES (SEQ ID NO: 1 has 3 mutations: $65/68 = 96\%$ homology; SEQ ID NO: 5 has 1 mutation: $68/69 = 99\%$ homology). Thus, the instant specification does not disclose any RANTES polypeptides that exhibit 90-94% homology to wild-type RANTES, contains at least one mutation in the dibasic site, has reduced GAG-binding activity, and has also been shown to be effective in treating an autoimmune, inflammatory, or infectious disease when orally administered to a subject. There are no limitations on the location(s) or region(s) of permissible mutations, other than the 40's dibasic region, and therefore the claims are drawn to administration of a genus of RANTES polypeptides that have not been adequately described in the specification.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the administered RANTES polypeptide has at least 90% homology

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to wild-type RANTES, contains at least one mutation in the 40's dibasic site, and has reduced GAG-binding activity. There is no identification of any particular portion of a RANTES polypeptide that must be conserved in order to maintain function, and no limitation on the position(s) or location(s) of potential mutations other than those in the 40's dibasic site. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

Rejections withdrawn

1. Rejection of claims 6-12 under 35 USC § 112, second paragraph, as being indefinite regarding mutants "and their *muteins*" as set forth on pages 9-10 of the prior office action mailed on 3/1/2006, is withdrawn in response to Applicant's cancellation of the claims.

Rejections necessitated by amendment

2. Claims 13-16 are indefinite because the elements recited in the claim do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

3. Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites "reduced GAG-binding activity." The acronym GAG is not defined upon the first use in the claims, and therefore the claims are indefinite.

4. Claims 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method of antagonizing the activity of RANTES. However, the claims do not define or recite a specific activity of RANTES that is to be antagonized, and therefore the metes and bounds of "antagonizing the activity of RANTES" cannot be determined.

5. Claims 13-33 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are drawn to: (1) a method of treating a disease by orally administering a RANTES polypeptide, (2) a method of antagonizing the activity of RANTES by orally administering a RANTES polypeptide, and (3) a method of administering a RANTES polypeptide to an individual. The claims do not recite a conclusion step that specifies or defines an intended effect or experimental end-point of the claimed methods.

Claim Rejections - 35 USC § 102

1. Rejection of claims 6-8 and 10-11 under 35 USC § 102(b), as being anticipated by Lusso and Polo, as set forth on pages 10-11 of the prior office action mailed on 11/3/2005, is withdrawn in response to Applicant's cancellation of the claims.

2. Rejection of claims 6-9 and 11 under 35 USC § 102(b), as being anticipated by Proudfoot *et al*, as set forth on pages 11 of the prior office action mailed on 11/3/2005, is withdrawn in response to Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 103

Rejections withdrawn

1. Rejection of claim 12 under 35 USC § 103, as being obvious over the combination of Lusso and Polo and Strieter *et al*, as set forth on pages 11-12 of the prior office action mailed on 10/07/2005, is withdrawn in response to Applicant's cancellation of the claim.

Rejections necessitated by amendment

2. Claims 13-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Proudfoot *et al* (as cited in the prior office action mailed on 11/3/2005) and Lusso and Polo (as cited in the prior office action mailed on 11/3/2005) in view of Czaplewski *et al* (US 5,965,697 - cited in the information disclosure statement received on 7/11/2005).

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The claims of the instant invention are drawn to methods of (1) treating a disease, (2) antagonizing the activity of RANTES, and (3) administration to an individual, comprising oral administration of a RANTES polypeptide that is at least 90% homologous to the wild-type RANTES, and contains at least one mutation in the 40's dibasic region. The claims are further drawn to oral administration of a RANTES polypeptide that has three or more substitutions at positions 44, 45, and 47, and specifically, oral administration of the polypeptide of SEQ ID NO: 1.

Proudfoot *et al* teaches a RANTES polypeptide produced by mutation of amino acids 44, 45, and 47, and specifically teaches a RANTES R44A-K45A-R47A triple mutant which is equivalent to the polypeptide of SEQ ID NO: 1. Thus, as is set forth on page 11 of the prior office action mailed on 11/3/2005, Proudfoot *et al* discloses a RANTES polypeptide with at least 90% homology to the wild-type RANTES and at least one mutation in the 40's dibasic site, and also teaches the polypeptide of SEQ ID NO: 1. The RANTES R44A-K45A-R47A polypeptide of Proudfoot *et al* was also disclosed as being able to inhibit HIV infectivity (p. 10623, 2nd column and Fig. 7). Proudfoot *et al* is silent regarding oral administration of any RANTES polypeptide.

Lusso and Polo, as set forth on page 10 of the prior office action mailed on 11/3/2005, disclose a RANTES polypeptide with at least 90% homology to the wild-type RANTES polypeptide and contains at least one mutation in the 40's dibasic site. Lusso and Polo also teach administration of compositions of RANTES polypeptides for treating various diseases, including HIV infection, inflammatory diseases, autoimmune disease such as rheumatoid arthritis, and allergic diseases such as asthma, rhinitis, and dermatitis (page 5, lines 2-4 and 17-22, and page 5, line 23 – page 6, line 5). Lusso and Polo is silent regarding oral administration of any RANTES polypeptide.

Czaplewski *et al* teaches various RANTES mutants, and further teaches administration of RANTES mutants for treatment of HIV infected individuals (column 13, lines 18-43). Czaplewski *et al* also discloses that diseases such as multiple sclerosis can also be treated by administration of RANTES (column 2, line 10-19). Furthermore, Czaplewski *et al* discloses administration of RANTES mutants by oral administration (column 14, lines 32-41).

Therefore, a person of ordinary skill in the art, at the time the instant invention was conceived, would have been motivated to practice a method of treating a disease, antagonizing the activity of RANTES, or of administering RANTES polypeptides to an individual, wherein said methods comprise orally administering a RANTES polypeptide with at least 90% homology to

the wild-type RANTES polypeptide and containing at least one mutation in the 40's dibasic site, or a RANTES polypeptide mutated at positions 44, 45, and 47, or the polypeptide of SEQ ID NO: 1. The motivation to do so comes from the teachings of Proudfoot *et al* and Lusso and Polo, which teach RANTES polypeptides meeting the limitations of the claims of the instant invention, and further teaching administration of RANTES mutant polypeptides for treating various diseases, including HIV infection, inflammatory disease, and autoimmune disease. Motivation for a method of oral administration comes from Czaplewski *et al*, which teaches that CC chemokines such as RANTES can be orally administered for the treatment of various diseases, including HIV infection and multiple sclerosis. Thus, the combination of Proudfoot *et al* or Lusso and Polo with Czaplewski *et al* provides a person of ordinary skill in the art with the knowledge of RANTES polypeptides that meet the claim limitations of the instant invention, and further teach the usefulness of these polypeptides in the treatment of disease, and teach the route of administration of the instant invention. Thus, the skilled artisan would also have a reasonable expectation of success in practicing the methods of the instant invention by combining the teachings of Proudfoot *et al*, Lusso and Polo, and Czaplewski *et al*. Furthermore, although Proudfoot *et al*, Lusso and Polo, and Czaplewski *et al* do not specifically recite antagonizing the activity of RANTES or treatment of bacterial infections, a method derived from the combination of the references would be expected, in the absence to the contrary, to be efficient in antagonizing RANTES activity and treating bacterial infections due to the exact similarity between SEQ ID NO: 1 of the instant application and the RANTES polypeptide taught by Proudfoot *et al*. The process steps of orally administering the RANTES mutants of the instant application or of Proudfoot *et al* or Lusso and Polo are the same regardless of whether the purpose of the method is to treat HIV infection, antagonize RANTES activity, or treat a bacterial infection (Ex parte Novitski, 26 USPQ 1391). The method of orally administering the RANTES polypeptides for treatment of HIV infection would inherently treat bacterial infection and/or antagonize the activity of RANTES.

Double Patenting

Rejections withdrawn

1. Rejection of claims 6-12 under the judicially-created doctrine of double patenting over claims 1-5 and 9 of co-pending Application No. 10/398,457, as set forth on pages 12-13 of the prior office action mailed on 11/3/2005, is withdrawn in response to Applicant's cancellation of the claims.

Rejections necessitated by amendment

2. Claims 13-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-12, 15-16, and 19 of copending Application No. 10/540,234. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant invention are drawn to methods of orally administering a RANTES polypeptide that is at least 90% homologous to wild-type RANTES and contains at least one mutation in the 40's dibasic site and having reduced GAG-binding activity. Claims 11-12, 15-16, and 19 of the '234 application are drawn to methods of treating inflammatory or autoimmune disease by administration of a RANTES mutant with reduced GAG-binding activity, and further recite administration of RANTES triple 40's mutants, and RANTES mutants in which one or more amino acids have been inserted or substituted.

It would be obvious to person of ordinary skill in the art to practice the methods of the instant invention by following claims 11-12, 15-16, and 19 of the '234 application. Both applications are drawn to the administration of RANTES polypeptides with reduced GAG-binding activity, and are further drawn to RANTES polypeptides with at least one mutation in the 40's dibasic site. Although the '234 application does not specifically recite oral administration, the language of the claims does not exclude this type of administration, and oral administration of pharmaceutical compositions is well-known in the art. Thus, by following the teachings of the '234 application, a skilled artisan would have both the motivation and a reasonable expectation of success in orally administering RANTES polypeptides with at least 90% homology to wild-type RANTES, and further having reduced GAG-binding activity and at least one mutation in the 40's dibasic site. Furthermore, although the '234 application does not specifically recite methods of antagonizing RANTES activity or methods of treating bacterial or viral infections, it would be expected, in the absence of contrary, that administration of the RANTES polypeptides taught by the '234 application would inherently antagonize RANTES activity and/or be effective in treating viral and bacterial infections.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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BDH
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A handwritten signature in black ink, appearing to read 'R. Landsman', with a large, stylized initial 'R'.

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER